Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2009

I. Background

As previously mentioned in the annual summary of fatalities reported to the FDA in Fiscal Years (FY) 2005 through FY2008, the blood supply is safer today than at any time in history. Due to advances in donor screening, improved viral marker tests, automated data systems, and changes in transfusion medicine practices, the risks associated with blood transfusion continue to decrease. Overall, the number of transfusion related fatalities reported to the FDA remains small in comparison to the total number of transfusions. In 2006, for example, there were approximately 30 million components transfused.[1] During the proximate period of FY2006, there were 73 reported transfusion related and potentially[2] transfusion related fatalities, with subsequent reports of 63 in FY2007, 54 in FY2008, and 66 in FY2009.

CBER is distributing this summary of transfusion fatality reports received by the FDA to make public the data received in FY2009, to provide the combined data received over the last five fiscal years, and to compare the FY2009 reports to the fatality reports received in the previous four fiscal years. We also include information on the infrequent reports of post-donation fatalities. Throughout this report we note changes over time, but the reader should interpret these changes cautiously, given the small numbers of reports and inherent variations in reporting accuracy. The significance of shifts in numbers derived from small populations may appear to be greater than they really are.

Refer to Sections 606.170(b) and 640.73 of Title 21, Code of Federal Regulations (21 CFR 606.170(b) and 21 CFR 640.73), for fatality reporting requirements. For information regarding the notification process, see our web page, Notification Process for Transfusion Related Fatalities and Donation Related Deaths, http://www.fda.gov/biologicsbloodvaccines/safetyavailability/reportaproblem/transfusiondonationfatalities/default.htm. For further information, see our *Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion*, September 2003.[3]

A team of CBER medical officers reviews the documentation submitted by the reporting facilities and obtained by FDA investigators, to assess the relationship, if any, between the blood donation or transfusion and the reported fatality.

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[1] Whitaker BI, Green J, et al. The 2007 Nationwide Blood Collection and Utilization Survey Report. Washington (DC): Department of Health and Human Services; 2008.

[2] Transfusion could not be ruled out as the cause of the fatality.

[3] Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion, September, 2003. http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/blood/ucm074947.htm.

If you have questions concerning this summary, you may contact us using any of the three following options.

1. Email us at fatalities2@fda.hhs.gov,
2. Call us at 301-827-6220, or
3. Write us at:
   FDA/Center for Biologics Evaluation and Research
   Office of Compliance and Biologics Quality
   Division of Inspections and Surveillance (HFM-650)
   1401 Rockville Pike, Suite 200 North
   Rockville, Maryland 20852-1448

II. Results

During FY2009 (October 1, 2008, through September 30, 2009), we received a total of 80 fatality reports. Of these reports, 74 were transfusion recipient fatalities and 6 were post-donation fatalities.

Of the 74 transfusion recipient fatality reports, we concluded:

a) 44 of the fatalities were transfusion-related,
b) 22 of the fatalities were cases that transfusion could not be ruled out as the cause of the fatality,
c) 8 of the fatalities were unrelated to the transfusion.

We summarize the results of our review in the following sections. Sections A through D of this document present the transfusion-related fatalities. Sections E and F and Table 5 present the fatality reports which were unrelated to the transfusion, or in which we could not rule out the transfusion as the cause of death. Section G presents the post-donation fatality reports.

A. Overall Comparison of Transfusion-Related Fatalities Reported from FY2005 through FY2009

In combined Fiscal Years (FY) 2005 through 2009, Transfusion Related Acute Lung Injury (TRALI) caused the highest number of reported fatalities (48%), followed by hemolytic transfusion reactions (26%) due to non-ABO (16%) and ABO (10%) incompatibilities.

Complications of microbial infection, Transfusion Associated Circulatory Overload (TACO), and anaphylactic reactions each accounted for a smaller number of reported fatalities (Table 1 and Figure 1). Over the last five fiscal years, we have seen an overall increase in reports of transfusion related TACO fatalities – from three reports in FY2008 to 12 reports in FY2009.[4] The number of transfusion related deaths due to anaphylaxis has remained very small over the last 5 years.

Table 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2009

Complication	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	FY09	FY09	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
TRALI	29	47%	35	56%	34*	65%	16*	35%	13*	30%	127	48%
HTR (non-ABO)	16	26%	9	14%	2	4%	7	15%	8	18%	42	16%
HTR (ABO)	6	10%	3	5%	3	6%	10	22%	4	9%	26	10%
Microbial Infection	8	13%	7	11%	6	12%	7	15%	5	11%	33	12%
TACO	1	2%	8	13%	5	10%	3	7%	12	27%	29	11%
Anaphylaxis	0	0%	1	2%	2	4%	3	7%	1	2%	7	3%
Other	2**	3%	0	0%	0	0%	0	0	1***	2%	3	1%
Totals	62	100%	63	100%	52	100%	46	100%	44	100%	267	100%

*In FY2007, our review committee began using the Canadian Consensus Conference criteria[5,6] for evaluating TRALI cases – these numbers includes both "TRALI" and "possible TRALI" cases

**Other: Includes one case of Graft vs. Host Disease (GVHD) and one therapeutic plasma exchange (TPE) error (use of a treatment column contraindicated due to patient's medical history)

***Other: Hypotensive Reaction[7]

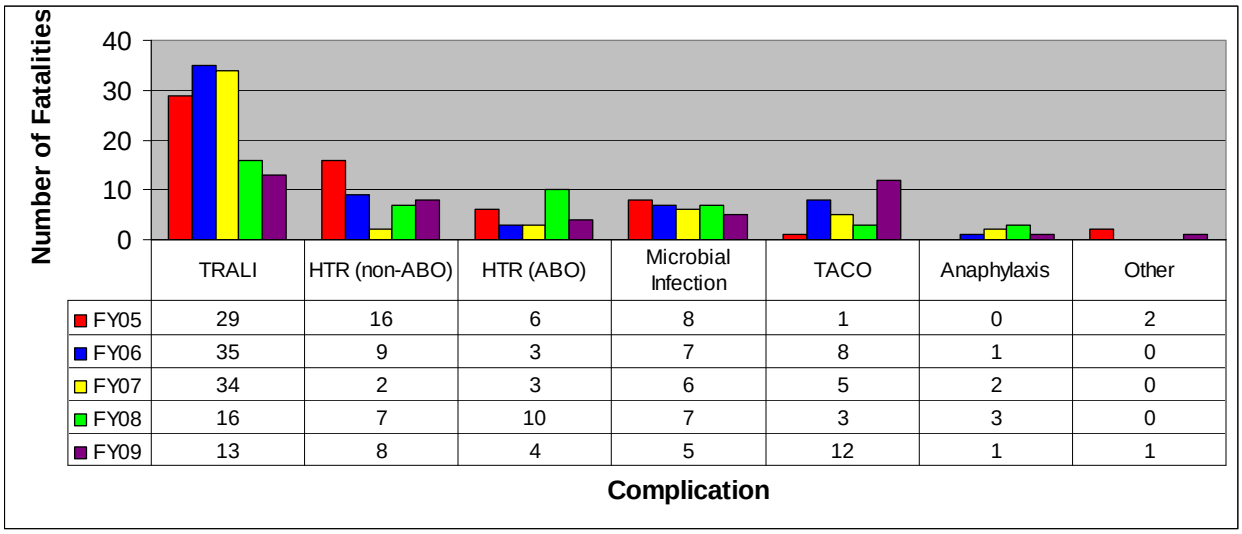
[4] Popovsky MA. Transfusion associated circulatory overload: the plot thickens. Transfusion 2009;49:2-4.

[5] Goldman M, Webert KE, Arnold DM. et al. Proceedings of a consensus conference: towards an understanding of TRALI. Transfus Med Rev 2005;19:2-31.

[6] Kleinman S, Caulfield T, Chan P, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 2004;44:1774-1789.

[7] Centers for Disease Control and Prevention. The National Healthcare Safety Network (NHSN) Biovigilance Component protocol. 2009:17.

Figure 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2009



	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY05	29	16	6	8	1	0	2
FY06	35	9	3	7	8	1	0
FY07	34	2	3	6	5	2	0
FY08	16	7	10	7	3	3	0
FY09	13	8	4	5	12	1	1

B. Transfusion Related Acute Lung Injury (TRALI)

While TRALI represented 48% of confirmed transfusion related fatalities reported to CBER over the last five fiscal years, fatalities due to TRALI have continued to decrease - to 30% of confirmed transfusion related fatalities in FY2009, compared to 35% in FY2008, and 65% in FY2007. The number of TRALI fatalities associated with receipt of Plasma products decreased from 12 (35% of TRALI cases) in FY2007, to 4 (25% of TRALI cases) in FY2008, to 3 in FY2009 (23% of TRALI cases) (Figure 2). TRALI fatalities associated with receipt of Apheresis Platelets decreased from 5 (31% of TRALI cases) in FY2008 to 2 (15% of TRALI cases) in FY2009.

In Calendar Year 2006, transfused plasma products accounted for approximately 13% of all transfused components, apheresis platelets (using platelet concentrate equivalent units) – approximately 30%, and red blood cell-containing products – approximately 49%.[8] In comparison, for the combined fiscal years 2005-2009, Fresh Frozen Plasma (FFP) and other plasma accounted for 46% (58/127) of reported TRALI fatalities, apheresis platelets accounted for 11% (14/127), and RBC's accounted for 26% (33/127).

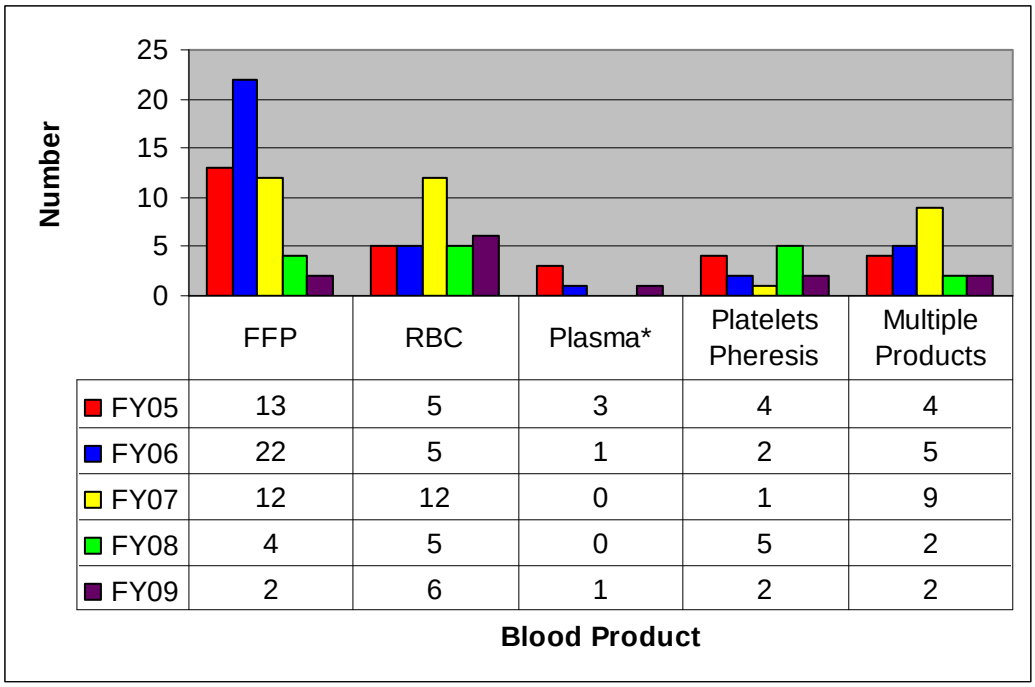
In FY2009, the 13 TRALI cases were temporally associated with products from 38 donors. Of the 38 implicated donors, 19 (50%) were tested for white blood cell (WBC) antibodies (Table 2). Antibody tests were negative in 42% of those tested. Of those tested, Human Leukocyte Antibodies (HLA) were present in 53% of donors. Human Neutrophil Antibodies (HNA) were present in 26% of donors (in two of these donors, no HNA specificity was determined). Some of the donors had multiple antibodies. Reporters who included patient testing data were able to match donor antibodies with recipient cognate antigens in 6 of the 13 cases, implicating 5 female donors and one male.

[8] Whittaker BI, op.cit. Tables 4-1 and 4-2.

Of the 38 implicated donors, reports identified 16 females (42%) and 22 males (58%). Of the 19 donors that were tested, 12 were females (10 with a history of pregnancy; 2 with unknown pregnancy history) and 7 were males (one with a history of transfusion; 6 with no reported history of transfusion or transplant). Nine of the 12 females tested positive for antibodies, implicating 6 RBC's, 1 FFP, and 2 Apheresis Platelets. Two of the 7 males tested positive for antibodies, implicating 1 FFP and 1 Plasma frozen within 24 hours after collection (FP24).

Although the transfusion community has taken voluntary measures to reduce the risk of TRALI, this complication of transfusion continues to be one of the leading causes of transfusion-related fatalities reported to the FDA. Current literature describes the results of continued international efforts to reduce the use of plasma for transfusion prepared from female donors.[9,10,11,12,13]

Figure 2: Reports of TRALI by Implicated Blood Product, FY2005 through FY2008



	FFP	RBC	Plasma*	Platelets Pheresis	Multiple Products
FY05	13	5	3	4	4
FY06	22	5	1	2	5
FY07	12	12	0	1	9
FY08	4	5	0	5	2
FY09	2	6	1	2	2

*FY2005: Includes 2 FP24 (Plasma frozen within 24 hours after collection) and 1 Liquid Plasma
*FY2006: Includes 1 FP24
*FY2009: Includes 1 FP24

[9] Eder AF, Benjamin RJ. TRALI risk reduction: donor and component management strategies. J Clin Apher 2009;24(3):122-9.
[10] Murphy MF, Navarete C, Massey E. Donor screening as a TRALI risk reduction strategy. Transfusion 2009;49:1779-82.
[11] Stillman CC, Fung YL, et al. Transfusion-related acute lung injury (TRALI): Current concepts and misconceptions. Blood Reviews 2009;23:245-255.
[12] Chapman CE, Stainsby D, et al. Serious Hazards of Transfusion Steering Group. Ten years of hemovigilance reports of transfusion related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. Transfusion 2009;49:440-52.
[13] Keller-Stanislawski B, Riel A, et al. Frequency and severity of transfusion-related acute lung injury – German haemovigilance data [2006-2007]. Vox Sang 2010;98:70-77.

Table 2: Donor Antibodies Identified in Association with TRALI, FY2007 through FY2009

Donor Leukocyte Antibodies	FY07 No.	FY07%	FY08 No.	FY08%	FY09 No.	FY09 %
HLA Class I	18	17%	3	18%	1	5%
HLA Class II	6	6%	2	12%	0	0%
HLA Class I and II	15	14%	6	35%	5	26%
HNA	17	16%	2	12%	1	5%
HLA and HNA	6	6%	2	12%	4	21%
Negative	42	41%	2	12%	8	42%
Total Donors Tested	104	100%	17	100%	19	100%

This table does not include the 59 donors that were not tested for WBC antibodies in FY07, the 3 donors that were not tested in FY08, and the 19 donors that were not tested in FY09.

C. Hemolytic Transfusion Reactions

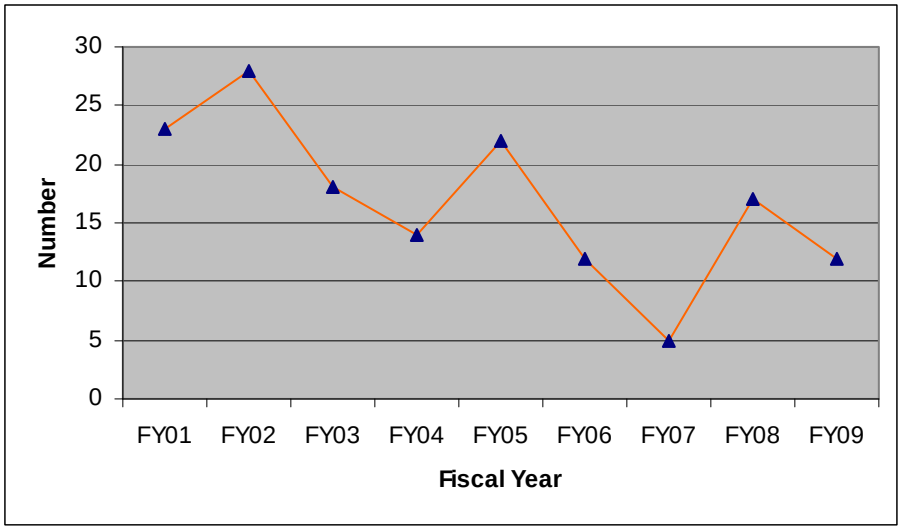
In FY2009, hemolytic transfusion reactions and TACO were the second leading causes of transfusion related fatalities reported to CBER, each representing 27% of confirmed transfusion related fatalities. The number of reported fatal hemolytic transfusion reactions decreased from 17 in FY2008 to 12 in FY2009, due to a decrease in reports of ABO hemolytic reactions, from 10 (59%) in FY2008, to 4 (33%) in FY2009 (Figure 1 and Table 3). We continue to see an overall decrease in the number of reported fatalities due to hemolytic transfusion reactions since FY2001 (Figure 3).

Table 3: Hemolytic Transfusion Reactions by Implicated Antibody, FY2005 through FY2009

	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	FY09	FY09	Total	Total
Antibody	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
ABO	6	27%	3	25%	3	60%	10	59%	4	33%	26	38%
Multiple Antibodies*	6	27%	4	33%	1	20%	1	6%	2	17%	14	21%
Jk^{b}	3	14%	0	0%	0	0%	2	12%	0	0%	5	7%
Other**	3	14%	0	0%	0	0%	0	0%	2	17%	5	7%
Kell	1	5%	1	8%	0	0%	2	12%	0	0%	4	6%
Jk^{a}	1	5%	1	8%	1	20%	0	0%	2	17%	5	7%
Fy^{a}	0	0%	1	8%	0	0%	2	12%	1	8%	4	6%
Fy^{b}	0	0%	1	8%	0	0%	0	0%	0	0%	1	1%
E	1	5%	0	0%	0	0%	0	0%	0	0%	1	1%
I	1	5%	0	0%	0	0%	0	0%	0	0%	1	1%
Js^{a}	0	0%	1	8%	0	0%	0	0%	0	0%	1	1%
Js^{b}	0	0%	0	0%	0	0%	0	0%	1	8%	1	1%
Totals	22	100%	12	100%	5	100%	17	100%	12	100%	68	100%

*FY2005 antibody combinations included E+c, Fy^a+K, Fy^a+Jk^b, E+I+A_1, possible C+E+K, Wr^a+warm autoantibody.
*FY2006 antibody combinations included E+c, S+K, Jk^b+cold agglutinin, unidentified auto- and alloantibodies.
*FY2007: anti-M+C
*FY2008: anti-C+K+Fy^b+S+N+V+Js^a+Go^a+warm autoantibody.
*FY2009: antibody combinations included E+Jkb, S+Jka+Jkb+K+Fya+Fyb+V+C+N+HTLA
**FY2005: Includes one report of non-immune hemolysis, one report of an unidentified antibody to a low incidence antigen, and one report of Cold Agglutinin Syndrome due to *Mycoplasma pneumonia* or Lymphoma.
**FY2009: Includes one report of an unidentified warm autoantibody and one report of Hyperhemolysis Syndrome[14]

Figure 3: Hemolytic Transfusion Reactions, FY2001 through FY2009



In FY2009, there were four reports of fatal hemolytic transfusion reactions due to ABO-incompatible blood transfusions:

- 1 case: recipient identification error at the time of transfusion (nursing error)
- 1 case: patient sample labels switched (phlebotomist error)
- 1 case: sample collected from incorrect patient (phlebotomist error)
- 1 case: patient sample mistyped (lab error)

[14] Win N, New H, et al. Hyperhemolysis syndrome in sickle cell disease: case report (recurrent episode) and literature review. Transfusion 2008;48:1231-1238

D. Microbial Infection

In FY2009, there were 5 reported fatalities attributed to microbial infection – similar to the numbers reported in the previous four fiscal years. Three different bacteria were implicated in three fatalities, and *Staphylococcus aureus* was implicated in two (40%) of the fatalities. Although *Babesia* accounted for 36% (10/28) of reported cases over the previous four fiscal years, there were no reported cases in FY2009. *Babesia* now accounts for 30% (10/33) of deaths due to microbial infection over the 5-year reporting period, followed by *Staphylococcus aureus*, which accounted for 21% (7/33) (Table 4).

After seven years with no reported deaths due to transfusion-transmitted Babesiosis, CBER received reports of 10 transfusion-transmitted Babesiosis deaths during fiscal years 2006 through 2008. Recent articles provide additional information about this topic.[15,16]

There was one strict anaerobe, *Eubacterium limosum,* implicated in a fatal bacterial infection during the 5-year reporting period; this fatality occurred in FY2005. The remaining bacteria are facultative anaerobes.

In FY2009, there were no reports of fatal microbial infections associated with Red Blood Cells, compared to 5 reports in FY2008, which were all due to *Babesia* infections. There was a small increase in the number of reports of fatal microbial infections associated with apheresis platelets[17] in FY2009 (Figure 4). However, this finding is still consistent with an overall decrease in the number of bacterial infections associated with apheresis platelets since FY2001 (Figure 5).

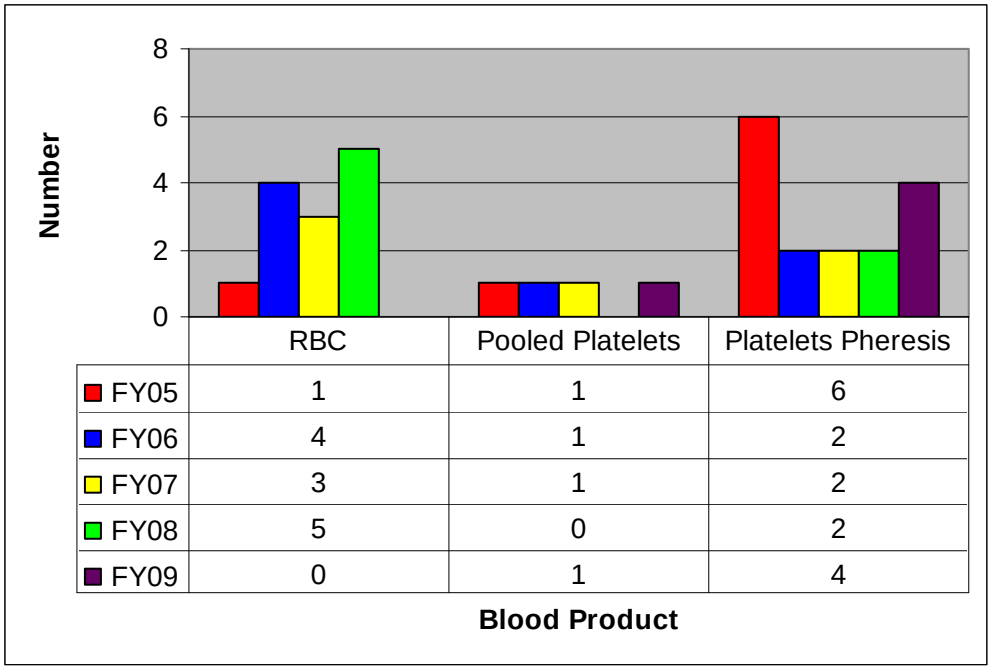
[15] Gubernot DM, Nakhasi HL, Mied PA, et al.Transfusion-transmitted babesiosis in the United States: summary of a workshop. Transfusion 2009;49:2759-2771.
[16] Tonetti L, Eder AE, Dy B, et al. Transfusion-transmitted *Babesia Microti* identified through hemovigilance. Transfusion 2009;49:2557-2563.
[17] Fuller AK, Uglik KM, et al. Bacterial culture reduces but does not eliminate the risk of septic transfusion reactions due to single-donor platelets. Transfusion 2009;49:2588-2593.

Table 4: Microbial Infection by Implicated Organism, FY2005 through FY2009

Organism	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	FY09	FY09	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
*Babesia**	0	0%	2	29%	3	50%	5	71%	0	0%	10	30%
Staphylococcus aureus	3	37%	0	0%	1	17%	1	14%	2	40%	7	21%
Escherichia coli	0	0%	3	43%	0	0%	0	0%	0	0%	3	9%
Serratia marcescens	2	24%	0	0%	0	0%	0	0%	0	0%	2	6%
Staphylococcus epidermidis	1	13%	0	0%	0	0%	1	14%	0	0%	2	6%
Staphylococcus lugdunensis	1	13%	0	0%	0	0%	0	0%	0	0%	1	3%
Eubacterium limosum	1	13%	0	0%	0	0%	0	0%	0	0%	1	3%
Morganella morganii	0	0%	1	14%	0	0%	0	0%	0	0%	1	3%
Yersinia enterocolitica	0	0%	1	14%	0	0%	0	0%	0	0%	1	3%
Streptococcus dysgalactiae (Group C)	0	0%	0	0%	1	17%	0	0%	0	0%	1	3%
Klebsiella oxytoca	0	0%	0	0%	1	17%	0	0%	0	0%	1	3%
Streptococcus viridans	0	0%	0	0%	0	0%	0	0%	1	20%	1	3%
Streptococcus pneumoniae	0	0%	0	0%	0	0%	0	0%	1	20%	1	3%
Staphylococcus warneri	0	0%	0	0%	0	0%	0	0%	1	20%	1	3%
Total	8	100%	7	100%	6	100%	7	100%	5	100%	33	100%

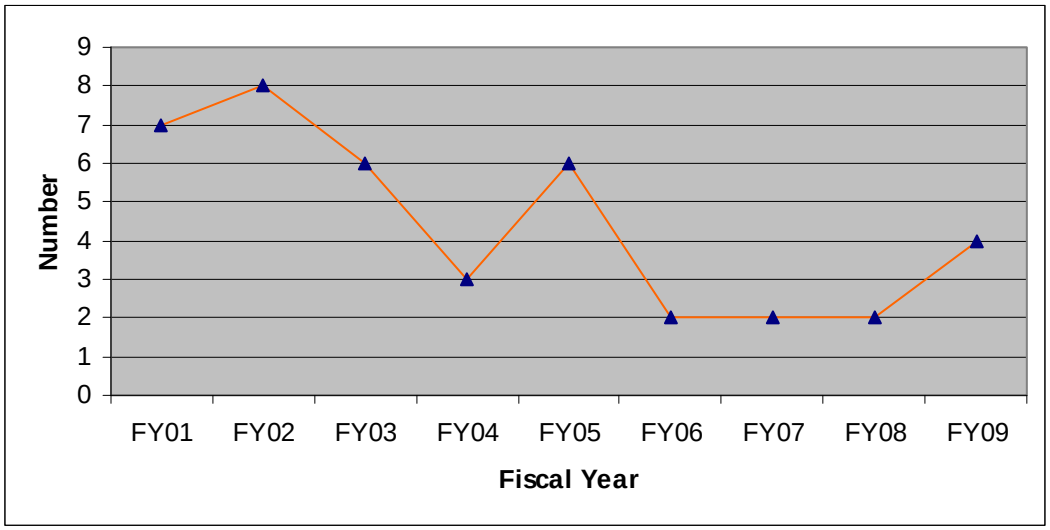
*Nine *Babesia microti* and one probable *Babesia MO-1* species

Figure 4: Microbial Infection by Implicated Blood Product, FY2005 through FY2009



Red Blood Cells microorganisms: *S. marcescens (1), E. coli (1), Y. enterocolitica (1), B. microti (9), B. MO1(1)*
Pooled Platelets microorganisms: *S. aureus (1), E. coli (1), S. dysgalactiae (1), S. pneumoniae (1)*
Platelets Pheresis microorganisms: *S. aureus (6), S. marcescens (1), S. lugdunensis (1), S. epidermidis (2), E. limosum (1), E. coli (1), M. morganii (1), K. oxytoca (1), S.viridans (1), S. warneri (1)*

Figure 5: Bacterial Infection by Apheresis Platelets, FY2001 through FY2009



E. Transfusion Not Ruled Out as Cause of Fatality

In these reported fatalities, the reporting facilities were unable to identify a specific complication of transfusion as the cause of death. Often, these patients had multiple co-morbidities, and after review of the investigation documentation, our medical reviewers could neither confirm nor rule out the transfusion as the cause of the fatality (Table 5). We did not include these reported fatalities in the analysis in Sections II.A through II.D (transfusion-related fatalities), above. Combining the transfusion related fatalities with those that our medical officers could not rule out, there was a total of 66 reported fatalities in FY2009, as compared to 54 in FY2008 and 63 in FY2007.

F. Not Transfusion Related

After reviewing the initial fatality reports and the investigation documentation, we categorized a number of reported fatalities as "Not Transfusion Related." Our medical reviewers concluded that, while there was a temporal relationship between transfusion and subsequent death of the recipient, there was no evidence to support a causal relationship (Table 5). Thus, we did not include these reported fatalities in the analysis in Sections II.A through II.D (transfusion-related fatalities), above.

Table 5: Fatalities Not Related to Transfusion or Transfusion Not Ruled Out, FY2005 through FY2009

	FY05	FY06	FY07	FY08	FY09
Not Transfusion Related	21	8	13	18	8
Not Ruled Out	14	10	11	8	22
Totals	35	18	24	26	30

G. Post-Donation Fatalities

FY2009 showed a continued decrease since FY2007, in the number of reported fatalities following Source Plasma donation (Table 6). In all of these cases (FY2005 through FY2009), our medical reviewers concluded that, while there was a temporal link between the donations and the fatalities, there was no evidence to support a causal relationship between the donations and subsequent death of the donors.

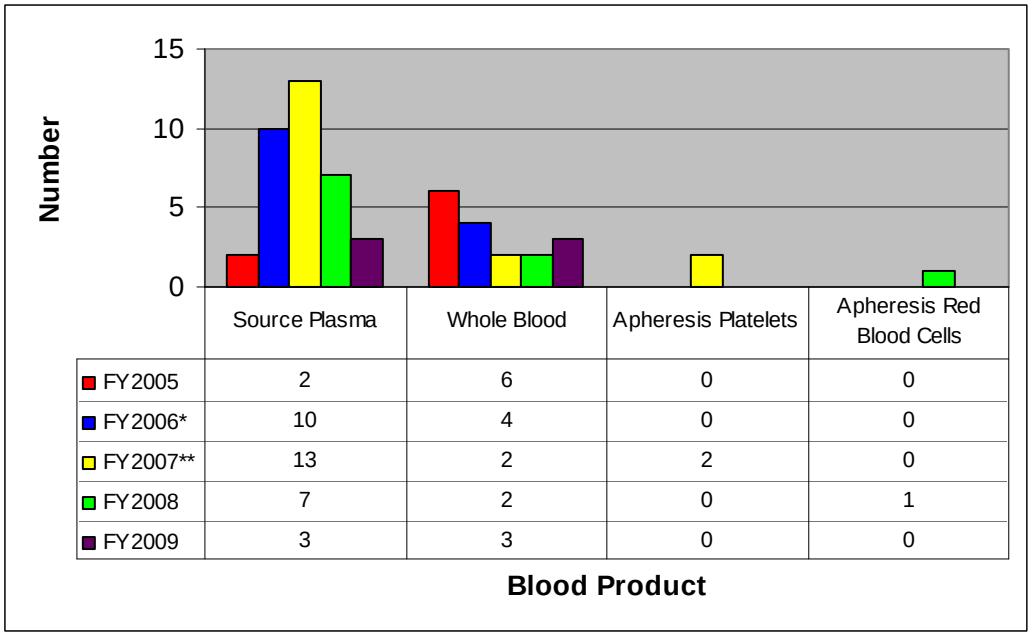
We received three FY2009 reports of fatalities following Whole Blood donation collected by manual methods. In two of these cases, our medical reviewers ruled out the donation as the cause of death due to evidence found in the donor's medical records. In the third case, although the donation could not be definitively ruled out as being implicated in the donor's death, our medical reviewers found no evidence to support a causal relationship between the donation and subsequent death of the donor.

Table 6: Post-Donation Fatality Reports by Donated Product, FY2005 through FY2009

Donated Product	FY05	FY06	FY07	FY08	FY09
Source Plasma	2	10	13	7	3
Whole Blood	6	4*	2**	2	3
Apheresis Platelets	0	0	2	0	0
Apheresis Red Blood Cells	0	0	0	1	0
Total	8	14	17	10	6

*Includes 2 autologous donations
**Autologous donations

Figure 6: Post-Donation Fatality Reports, FY2005 through FY2009



*Includes 2 autologous Whole Blood donations
**Both Whole Blood donations in FY07 were autologous